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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,288	01/16/2004	Marc Elliot Rothenberg	CMC -163	7158

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WOOD, HERRON & EVANS, LLP
2700 CAREW TOWER
441 VINE STREET
CINCINNATI, OH 45202

EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,288	ROTHENBERG, MARC ELLIOT	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-21 and 23-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/07/2004 & 07/16/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-37 are pending.

2. Applicant's election of claim 22, Group XXVII, now claims 22 and 32-37, in the reply filed on 12/06/2006 is acknowledged. Upon further consideration, the Examiner has withdrawn the restriction requirement, as requested by applicant, between Groups XXVII and XXVIII.

3. Claims 1-21 and 23-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 22 and 32-37 are currently under examination as they read upon physiological method comprising providing trefoil-factor 2 (TFF2) in a pharmaceutically acceptable composition to a lung of a patient in an amount sufficient to cause at least one of reduced lung acidity or enhanced lung epithelial cell repair.

5. Applicant is claiming priority to provisional application 60/440,934 with two inventors. Only one inventor is listed in the current application that claims the same subject matter.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "at least one of lung fluid, lung biopsy, sputum, mucus, nasal washings, respiratory tract tissue, respiratory tract fluid, or blood" lacks antecedent basis in base claim 22. Base claim 22 only recites at least one of reduced lung acidity or epithelial cell repair.

In Claim 37, it is unclear what is detected in the lung fluid, lung biopsy, sputum, mucus, nasal washings, respiratory tract tissue, respiratory tract fluid, or blood to determine lung acidity or enhanced lung epithelial cell repair. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized and a correlation step describing how the results of the assay allow for the determination.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 22 and 32-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection.**

The phrases "physiological method" and deletion of "thereby treating lung inflammation" claimed in claim 22, "wherein the composition is provided to a lung by a rout selected from the group consisting of intravenously, intranasally, intratracheally, subcutaneously, intramuscularly, orally, intraperitoneally and combinatins thereof" claimed in claim 32; "wherein the composition is formulated as at least one of aerosol, drops, tablets, capsules, pills, syrups, elixirs, emulsions, or suspensions" claimed in claim 33; "wherein the composition is provided to at least one of airway, trachea or bronchoalveoli claimed in claim 34; "wherein the composition is provided to the lung of an allergic patient" claimed in claim 35; "wherein the composition is provided to the lung of an asthmatic patient" claimed in claim 36; and "wherein at least one of lung fluid, lung biopsy, sputum, mucus, nasal washings, respiratory tract tissue, respiratory tract fluid or blood is assessed for reduced lung acidity or enhanced lung epithelial cell repair" claimed in claim 37 represent a departure from the specification and claims as originally filed.

Applicant's amendment filed on 12/06/2006 points to the specification at page 18 lines 16-24, page 19, lines 6 and 14-16 and original claims 7, 14, 15 and 17 for support for the newly added limitations. However, the specification does not provide clear support for such limitations.

The methods of physiological assessment of the patient's level of TFF2 is not equivalent to the claimed "physiological method." Further, the physiological assessment of a patient's TFF2 levels is done in vitro using southern, northern or western blots whereas the instant method of

claim 22 requires administration of TFF2 protein in vivo. In particular, on page 3, line 14 of the specification, "physiological method" refers to a method for determining the level of TFF2, not to a method of providing TFF2 a pharmaceutically acceptable composition to a patient. The specification only discloses administering TFF2 to a patient on page 3, lines 21-24 and page 19, lines 12-14 in the prophylactic or therapeutic method of providing TFF2 in a pharmaceutically acceptable composition to the lung for reducing lung pH, to treat lung inflammation or to enhance epithelial repair in the lung to treat lung inflammation.

Further, on page 4, lines 1-4 and page 20, lines 9-11, the prophylactic or therapeutic method of providing TFF2 in a pharmaceutically acceptable composition to the lung is for reducing lung pH to treat lung inflammation or to enhance epithelial repair in the lung **to treat lung inflammation**. The deletion of 'thereby treating lung inflammation' is new matter.

The specification discloses on page 19, lines 12-16 that **the evaluation of TFF2 levels and regulation of TFF2 expression** may occur in various organs such as in asthma, airway, lung, trachea, respiratory tract tissue, respiratory fluid, throat, mucus, nasal washings, and/or bronchoalveolar lavage lung fluid. In particular, "TFF2 may be determined in lung fluid, lung biopsy specimens, sputum, mucus, nasal washings, and/or blood" as disclosed on page 3, lines 16-17 the specification; and TFF2 expression is regulated by administering compositions affecting TFF2 including "small molecule inhibitors, anti-sense inhibitors, and/or transcriptional inhibitors of STAT6 or Th2 cytokine inhibitors" as disclosed on page 18, lines 14-24. In

addition, the specification disclose that the TFF2 regulating compositions may be administered to a patient with asthmatic symptoms and/or allergic symptoms and that the administration may be by inhalation, aerosol, drops, an enteral or parenteral route such as intravenous injection, subcutaneous injection, intramuscular injection, intraperitoneal injection, oral administration in a formulation in solid or liquid form, tablets, capsules, pills, syrups, elixirs, emulsions and suspensions. The specification does not contemplate 1.) the administration of TFF2 protein to a patient with allergic and/or asthmatic symptoms 2.) the administration of TFF2 protein in any specific formulation; or 3.) the administration to TFF2 by any specified route other than to a lung. The specification discloses only the administration of **compositions affecting TFF2** by these routes in these formulations for these purposes. Administering **compositions comprising TFF2** itself by these routes in these formulations for these purposes was not disclosed.

The specification does not disclose that the method of claim 22 further includes an assessment of reduced lung acidity or enhanced lung epithelial cell repair as recited in claim 37. The specification only discloses the prophylactic or therapeutic method of providing TFF2 in a pharmaceutically acceptable composition to the lung for reducing lung pH, to treat lung inflammation or to enhance epithelial repair in the lung to treat lung inflammation.

The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

Obviousness is not the standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977). New Matter is a written description issue.

10. Claims 22 and 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for **a physiological method for a patient comprising providing trefoil-factor-2 (TFF2) in a pharmaceutically acceptable composition to a lung of a patient in an amount sufficient to cause at least one of reduced lung acidity or enhanced lung epithelial cell repair of claim 22; wherein the composition is provided to a lung by a route selected from the group consisting of intravenously, intranasally, intratracheally, subcutaneously, intramuscularly, orally, intraperitoneally and combinatins thereof of claim 32; wherein the composition is formulated as at least one of aerosol, drops, tablets, capsules, pills, syrups, elixirs, emulsions, or suspensions" of claim 33; wherein the composition is provided to at least one of airway, trachea or bronchoalveoli of claim 34; wherein the composition is provided to the lung of an allergic patient of claim 35; wherein the composition is provided to the lung of an asthmatic patient of claim 36; or wherein at least one of lung fluid, lung biopsy, sputum, mucus, nasal washings, respiratory tract tissue, respiratory tract fluid or blood is assessed for reduced lung acidity or enhanced lung epithelial cell repair of claim 37.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses a method of providing TFF2 in a pharmaceutically acceptable composition to the lung whereby the method may reduce lung pH and/or enhance epithelial cell repair to treat lung inflammation. Supporting data includes a DNA microarray analysis demonstrating that TFF2 is an allergen-induced gene in asthmatic lung and a Northern blot analysis showing that TFF2 expression is induced by IL-4 and IL-13.

TFF2 has been associated with epithelial proliferation and acid production in the gastrointestinal tract in a pathogenic mechanisms causing ulceration, but has never been implicated in the pathogenesis of asthma.

There is insufficient guidance in the working examples to show that the administration of TFF2 to a patient can cause a reduction of lung pH or an enhancement of epithelial cell repair because there is no in vivo data disclosed where TFF2 is administered to any patient by any means.

The role of TFF2 in inflammatory responses in the lung has been questioned by Applicant's own data (PTO-892, Reference U, abstract). The reference teaches that the loss of TFF2 does not affect gross levels of tissue inflammation in an experimental mouse model of asthma. The reference data shows that TFF2 does not affect induction or resolution of goblet cell metaplasia or mucus production, as was hypothesized in the specification on page 16 lines 8-11. The reference teaches that the action of TFF2 in the gastrointestinal tract is not similar to the action of TFF2 in the lung, particularly with regard to asthma-induced pathology. Therefore, using TFF2 as a therapy for asthma is highly unpredictable in the art.

The prior art also teaches that the method used for delivering asthma drugs to a patient depends on many factors (PTO-892, Reference V). For example, only 10% of the drug delivered by inhalation reaches airways below the larnyx (In particular, page 504, 'Metered dose inhalers' section). The rest is swallowed and absorbed in the gastrointestinal tract, which in the case of TFF2 which is also associated with gastrointestinal pathology, could have undesired side effects. Other drugs, such as theophyllines and leukotrienes cannot be inhaled effectively and must be given orally (In particular, page 506, 'Tablets and syrups' section). Therefore, the route of administration of drugs is highly unpredictable and would require undue experimentation.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 22 and 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/102399 (Reference AM, IDS filed on 07/16/2004).

WO 02/102399 teaches the administration of an effective amount of TFF2 polypeptide to provide a prophylactic and protective treatment for diseases including asthma or allergic rhinitis (In particular, claims 1-6 and 12; page 4, line 4; page 5, lines 5-10; page 6, lines 6-7; and page 8, line 12). The reference discloses TFF2 pharmaceutical composition delivered by luminal (airway, trachea or bronchoalveoli), parenteral and oral administration for the treatment of the

respiratory passages and respiratory tract (lung) (In particular, page 5, lines 16-19 and 34-35; and page 6 lines 8-9). The composition may be in a form suited for systemic injection or infusion (emulsions or suspensions) (In particular, pages 13, line 30 to page 14, line 5) or in droplets (drops) (In particular, page 7, lines 24-25).

The reference teachings anticipate the claimed invention.

13. Claims 22 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/38712 (PTO-892, Reference N).

WO 97/38712 teaches using intestinal trefoil polypeptide (ITF) including human spasmolytic peptide (TFF2) to promote the maintenance of mucosal integrity, inhibition of lesion formation and lesions healing in the respiratory tract (In particular, page 8, lines 8-10, pages 11, lines 21-33, claims 1-4, 21 and 26). The reference teaches a method for treating lesions of the respiratory epithelium in a mammal, such as a human, by administering a composition in a therapeutic amount of a trefoil peptide, including human spasmolytic peptide (TFF2) (In particular, page 11, lines 3-9, page 14, lines 30-35, page 36, lines 1-20). The composition is administered by inhalation of aerosol spray using a metered dose inhaler or dry powder inhaler (provided to at least one of airway, trachea, or bronchoalveoli) (In particular, page 37, line 31; page 39, lines 8-21). The reference method of treating respiratory lesions encompasses the claimed physiological method of providing TFF2 to a patient lung.

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 1, 2007

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

Maher M. Haddad

MAHER M. HADDAD
PRIMARY EXAMINER